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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,880	LEE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18,20-55,57,61-93 and 96-107* is/are pending in the application.

4a) Of the above claim(s) *11-18,20-48,50,65-78,80 and 89-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49,51-55,57,61-64,79,81-88 and 96-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/11/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 7/8/2009, in which claims 1-10, 19, 58 and 60 were canceled, claims 49, 52, 53, 57, 61, 63, 79, 96 and 97 were amended, and claims 98-107 were newly added. Currently claims 11-18, 20-55, 57, 61-93 and 96-107 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group III with traverse in the reply filed 6/21/2006. Applicant further elected the combination of biomarkers comprising SEQ ID NOs: 1, 2, 5, 15 and 16 (IL-8, COX-2, SAA1, PPAR-alpha and PPAR-gamma, respectively), and the oligonucleotide primers comprising SEQ ID NOs: 45 and 46, which amplify SEQ ID NO: 1; SEQ ID NOs: 47 and 48, which amplify SEQ ID NO: 2; SEQ ID NOs: 53 and 54, which amplify SEQ ID NO: 5; SEQ ID NOs: 73 and 74, which amplify SEQ ID NO: 15; and SEQ ID NOs: 75 and 76, which amplify SEQ ID NO: 16.

In the Office action mailed 9/11/2006, the Examiner withdrew the restriction requirement between Groups III and V. Although the restriction requirement mailed 5/5/2006 required an election of a single invention, which is one combination of sequences, the record indicates that claims reading on less then the full combination of sequences have been examined. Thus, the claims will be considered as they read at least two sequences selected from the group consisting

of SEQ ID NOs: 1, 2 and 5, as well as sequences selected from SEQ ID NOs: 15 and 16. The other combinations of sequences remain withdrawn.

Claims 11-18, 20-48, 50, 65-78, 80 and 89-93 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/21/2006.

Claims 49, 51-55, 57, 61-64, 79, 81-88, 96-107 are under consideration.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 6/11/2009, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Claim Objections

Claim 49 is objected to because of the following informalities: the term "multivariate" is misspelled. Claims 51-55, 57, 61-64, 96 and 97 depend from claim 49 and are objected to for the same reason applied to claim 49. Appropriate correction is required.

Claim 99 is objected to because of the following informalities: the claim reads on non-elected invention. Appropriate correction is not required at this time.

Response to Arguments - Claim Objections

The previous objections of claims 52, 53, 96 and 97 have been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/8/2009.

The objection of claim 60 is moot in view of Applicant's cancellation of the claim in the reply filed 7/8/2009.

Terminal Disclaimer

The terminal disclaimer filed on 7/8/2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted from Application Number 11/827,894 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Arguments - Double Patenting

The provisional rejection of claims 49, 51-53, 60, 61, 63 and 64, on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-6 of copending Application No. 12/180,347 ('347 application), has been withdrawn in view of the amendment to the claims in the '347 application.

The provisional rejection of claims 49, 54 and 60-62 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 104-107 of copending Application No. 11/827,894 has been withdrawn in view of the proper terminal disclaimer.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 51-55, 57, 61-64 and 96-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (A) A method for assessing the risk of colorectal polyps and colorectal cancer in a subject, comprising (i) obtaining a biological colorectal sample from the subject; (ii) isolating cellular RNA from the sample; (iii) amplifying and quantifying RNA expression levels for SEQ ID NOs: 1 and 2; (iv) comparing the quantified expression levels of SEQ ID NOs: 1 and 2 in the sample from the subject to expression of SEQ ID NOs: 1 and 2 in normal control colorectal samples; and (v) determining an increased risk of colorectal polyps and colorectal cancer in the subject when at least one of SEQ ID NOs: 1 and 2 is increased in expression in the sample from the subject as compared to the normal controls, does not reasonably provide enablement for using the method for determination of colorectal polyps and colorectal cancer (i.e., diagnosis), or management of colorectal polyps and colorectal cancer, which includes estimating risk, early diagnosis, establishing prognosis, monitoring patient treatment, or detecting relapse; using any change (increase or decrease) in expression levels to determine (increase or decreased) risk; or using biomarkers selected from SEQ ID NOs: 5, 15 and 16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was made in the Office action mailed 1/8/2009 and has been extended to new claims 98-107.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands

factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: Claims 49, 51-55, 57, 61-64, 96 and 97 are drawn to a method for "assessing the risk of colorectal cancer and colorectal polyps"; however, the gene expression levels are used by the method are to be "indicative of a colorectal cancer and colorectal polyps." Dependent claim 57 requires the use of the gene expression levels to identify a subject as a candidate for the risk management of colorectal cancer and colorectal polyps wherein the management is selected from one or more of risk assessment, early diagnosis, establishing prognosis, monitoring patient treatment for any treatment, and detecting relapse. Independent claim 49 is drawn to the steps of (i) selecting a panel of biomarkers comprising at least two polynucleotides selected from the group consisting of SEQ ID NOs: 1, 2 and 5; (ii) amplifying and quantifying RNA expression levels in a biological colorectal sample from a subject for each biomarker in the panel comprising the at least two polynucleotides selected from the group consisting of SEQ ID NOs: 1, 2 and 5; and (iii) comparing the quantified expression levels of each biomarker including the at least two polynucleotides in the sample to each of the same biomarker expression level in a normal control colorectal sample, wherein a difference when analyzed by a multivariate analysis of variance (MANOVA) in the expression levels in the biological sample compared to the normal control is indicative of colorectal cancer and colorectal polyps. The claims read on any difference in expression as being indicative of colorectal cancer and colorectal polyps. Claim 57 requires an increase in at least one biomarker of the selected biomarker panel in the sample compared to levels of the corresponding biomarkers from the normal control to identify the subject as a candidate for the management of

colorectal cancer and colorectal polyps. Claim 96 limits the at least one cDNA of claim 57 to a cDNA comprising SEQ ID NO: 1. Claim 97 limits the at least one cDNA to a cDNA comprising SEQ ID NO: 2.

Dependent claims 51-55 further limit the step of amplifying and quantifying RNA expression levels. Claim 51 indicates that the panel of biomarkers further comprises at least one polynucleotide from SEQ ID NOs: 15 and 16. Claim 52 further limits the amplifying step to one that uses at least two sets of primers chosen from (i) SEQ ID NO: 45 and 46; (ii) SEQ ID NO: 47 and 48; (iii) SEQ ID NO: 53 and 54; (iv) SEQ ID NO: 73 and 74; and (v) SEQ ID NO: 75 and 76. Claim 53 limits the step of amplifying to the use of enzymes and reagents for the preparation of cDNAs. Claim 54 limits the step of quantifying to further comprising labeling cDNA. Claim 55 limits the labeling to the inclusion of at least one chromophore.

Dependent claims 61-64 further limit the step of obtaining the sample. Claim 61 requires the step of obtaining to be minimally invasive or non-invasive. Claim 62 requires the minimally invasive step to be by use of a swab. Claim 63 requires the step of obtaining to be non-invasive, and claim 64 limits the non-invasive step to collection of a stool sample.

Claims 98-106 are drawn to a method for assessing the risk of colorectal cancer, comprising (i) selecting a panel of biomarkers comprising polynucleotides having sequences selected from the group consisting of SEQ ID NOs: 1 and 2; (ii) obtaining a biological colorectal sample from a subject; (iii) isolating cellular RNA from the sample; (iv) amplifying and quantifying RNA expression levels in a biological colorectal sample from a subject for each biomarker in the panel; and (v) comparing the quantified expression levels of each biomarker in the sample to each of the same biomarker expression level in a normal control colorectal sample,

wherein a difference in the expression levels in the biological sample compared to the normal control is indicative of colorectal cancer. The nature of the invention is complex in that one is only required to measure the expression of one of the biomarkers. Claim 99 requires the further measurement of additional biomarkers selected from SEQ ID NOs: 5, 15 and 16. Claim 102 requires an increase in one of the two biomarkers to identify the subject as a candidate for further clinical management including one or more of follow on risk assessment, patient monitoring, and detecting recurrence. The nature of the invention is complex in that the claims encompass the comparison of a single test subject to a single control subject, and the claims encompass any increase or decrease in expression of the biomarkers to predict any increase or decrease in risk. Moreover, the "wherein" clause of the method requires the expression levels to be "indicative of a colorectal cancer."

Claim 107 is drawn to a method for "determination of colorectal cancer and colorectal polyps." The "determination of colorectal cancer and colorectal polyps" is reasonably construed as diagnosis of colorectal cancer and colorectal polyps. Furthermore, the "wherein" clause is consistent with this interpretation in that it requires the expression levels to be "indicative of a colorectal cancer." Claim 107 is drawn to the steps of (i) selecting a panel of biomarkers comprising polynucleotides having sequences selected from the group consisting of SEQ ID NOs: 1 and 2; (ii) amplifying and quantifying RNA expression levels in a biological colorectal sample from a subject for each biomarker in the panel; and (iii) comparing the quantified expression levels of each biomarker in the sample to each of the same biomarker expression level in a normal control sample, wherein a difference in the expression levels in the biological sample compared to the normal control is indicative of a colorectal cancer. The nature of the

invention is complex in that the claims encompass the comparison of a single test subject to a single control subject, and the claims encompass any increase or decrease in expression of the biomarkers to diagnose colorectal cancer.

The invention is complex in that it involves measuring a change in the level of RNA by amplification, such that a determination of diagnosis or risk of colorectal cancer and colorectal polyps is made. The present specification teaches that the two criteria for assessing the effectiveness of biomarkers are selectivity and sensitivity, where selectivity refers to the percentage of patients correctly diagnosed, and sensitivity is defined as the probability that the disease is detected at a curable stage (e.g., paragraph [0014]). The specification teaches that there is a difference between diagnosis and risk assessment. The specification states the following at paragraph [0029]:

> The difference between risk assessment and early detection is the degree of certainty regarding acquiring CRC. Biomarkers that are used for early detection confer less than 100% certainty of CRC within a time interval, whereas biomarkers used for early detection confer an almost 100% certainty of the onset of the disease within a specified time interval.

The nature of the invention is complex in that the claims require the use of RNA expression levels of the claimed biomarkers to diagnose colorectal polyps and colorectal carcinoma. Thus, the biomarkers must confer an almost 100% certainty of the onset of the disease within a specified time interval. The occurrence of adenomous polyps are a necessary, but not sufficient condition for an individual to later develop colorectal cancer; 90% of all preinvasive cancerous lesion are adenomous polyps or precursors, but not all individuals with adenomous polyps go on to later develop colorectal cancer (e.g., specification, paragraph [0029]). The claims encompass the diagnosis of colorectal polyps and carcinoma. Given the

relationship between polyps and carcinoma, the claims are essentially encompassing the diagnosis of colorectal carcinoma that has developed from polyps. The RNA expression levels must be able to distinguish between subjects with polyps only and those with polyps and cancer to diagnose cancer, because not every subject with polyps will have cancer.

Furthermore, the claims encompass the use of the diagnosis to perform risk assessment, early diagnosis, establishing prognosis, monitoring patient treatment, and detecting relapse of colorectal polyps and colorectal cancer. Thus one must know how to use the RNA expression levels of the claimed biomarkers as a class predictor for risk status, response to treatment, and presence or absence of relapse.

Breadth of the claims: The claims are broad in that they encompass any increase or decrease in expression to determine (i) any increase or decrease in risk or (ii) the presence of colorectal cancer. The claims are broad in that they encompass the use of the method for diagnosis, early diagnosis, establishing prognosis, monitoring patient treatment, and detecting relapse of colorectal polyps and colorectal cancer. Furthermore, the claims encompass any difference in expression levels between the biological colorectal sample from the test subject and the normal control in that there may be any increase or decrease in expression of any two biomarkers selected from the group consisting of SEQ ID NOs: 1, 2 and 5 or at least two biomarkers selected from the group consisting of SEQ ID NOs: 1, 2 and 5 and at least one polynucleotide from SEQ ID NOs: 15 and 16.

Guidance of the specification/The existence of working examples: The specification discloses the use of a mouse multiple intestinal neoplasia (MIN) model to determine expression differences between mouse MIN subjects comprising a chemically induced mutation in the APC

gene and normal control littermates for which there was not aberration of the APC gene (page 5, paragraph 18). From these studies candidate genes were selected for study in human subjects; and from these studies with human samples, a disclosed panel of biomarkers was obtained. In one disclosed example, a panel of six biomarkers is used "as the basis for determination of CRC in human subjects" -- although the biomarkers were applied to samples obtained from patients known to have CRC and from individuals validated as normal controls (page 8, paragraph 27). The results are shown in Figure 2B for the panel of six markers, which include IL-8 (SEQ ID NO: 1), and COX2 (SEQ ID NO: 2), but does not include the markers of SEQ ID NO: 5, 15 or 16. In another example, multiple biopsy samples taken from one exemplary patient diagnosed with CRC showed differences in expression of three biomarkers (see paragraph bridging pages 9 and 10). However, the specification gives no indication of what such a difference in expression means for patient care management or for the discovery of therapeutic interventions. In the last example, the specification teaches that multiple biopsies (again from a single patient), taken over a 53 cm region of the colon, where able to "distinguish differences in the colon tissue for the patient" whereas the same biopsy samples were rendered normal by conventional histological analysis. The specification teaches that such results demonstrate a minimally invasive swabbing collection method from an area distant from a cancerous lesion is capable of indicating a "non-normal colon condition" (page 10, paragraph 32).

The specification does not provide a working example of the claimed method where a subject is diagnosed with colorectal polyps and colorectal cancer based upon the RNA expression levels of any two of the claimed biomarkers or where risk is determined. Thus, the specification does not teach the clinical selectivity and specificity of the test. The specification

fails to teach how measurements of RNA expression can be used to manage patient care or to discover new therapeutic interventions. The specification lacks a single example of the use of expression levels of SEQ ID NOs: 1, 2 or 5 in combination to manage patient care or to discover new inventions for CRC or colorectal polyps.

The specification does not teach what differences in expression of SEQ ID NOs: 1, 2 or 5 can be used in order to perform early diagnosis, establishing a prognosis, monitoring patient treatment or detecting relapse. For example, does an increase or decrease in the level of SEQ ID NOs: 1, 2 or 5 indicate that a relapse is likely? How much of an increase or decrease is required for such a conclusion to be reached?

In addition, it is acknowledged in the specification that "there is a distinct difference between research on a specific a gene, its expression, protein product, and regulation, and understanding what genes are critical to include in a panel used to for the analysis of CRC that is useful in the management of patient care for the disease." (paragraph 0017) and the application demonstrates that there is substantial variation in expression levels of individual genes when compared with control sample (paragraph 0027), which necessitates the use of a panel of biomarkers for diagnostic validity. In spite of this, the application seeks to claim a method of using all panels of biomarkers comprising any two of SEQ ID NO: 1, 2 or 5 to determine colorectal cancer or colorectal polyps and seeks to claim a method wherein an increase in a single cDNA identifies a subject as a candidate for the management of colorectal cancer.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of

a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The physiological art is recognized as unpredictable. (MPEP 2164.03.) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In the instant case, the specification teaches that "given the complexity of biological systems, discovery of panels useful in providing value in patient care management for CRC is in the nascent stage" (page 5, paragraph 16). The prior art supports this statement.

In general, the prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. The art teaches that before a putative biomarker can be used as a surrogate endpoint it must be validated as such. Wagner (2002) *Dis. Markers* 18:41-46 acknowledges in the Abstract, "Putative biomarkers are typically identified because of a relationship to known or hypothetical steps in a pathophysiologic cascade. Biomarker discovery can also be effected by expression profiling experiment using a variety of array technologies and related methods." However, Wagner cautions, "A rational basis for recommending the use of a

putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging the left and right columns on page 43) and "Biomarkers require validation in most circumstances" (paragraph bridging pages 43-44).

Frank *et al.* (2003) *Nature Rev.* 2:566-580 concurs, stating, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action" (paragraph bridging the left and right columns on page 568). Feng *et al.* (2004) *Pharmacogenomics* 5:709-719 teaches, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation…A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract).

The unpredictability of correlating gene expression level to any phenotypic quality is also supported by the teachings of Wu (*J. Pathol.* **195**(1):53-65, 2001.). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the

particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 – Discussion).

Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, Vol. 18, page 20, 2004) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (e.g. page 3, 2nd paragraph).

In post-filing art, Barrier et al (*Oncogene* 24:6155-6164, 2005; IDS Ref) teach the attempted construction of a prognosis predictor model for stage II and stage III colon cancer based on gene expression measurements that involve a number of genes, but which do not involve the claimed panel of biomarkers (see entire document, especially pages 6156-6158). However, Barrier concedes that the results of the study only "suggest the possibility to build an accurate prognosis predictor using gene expression profiles" and that the study "has to be confirmed by larger other studies" (see page 6162, first full paragraph). In other post-filing art, Hao et al (*Clinical Cancer Research* **11**:1400-1407, 2005; IDS Ref.) teach that gene expression of the claimed sequences is altered in macroscopically normal colonic mucosa from individuals with a family history of sporadic colon cancer, but that prospective studies will be needed "to determine whether or not altered gene expression is associated with the subsequent development

of adenomatous polyps and/or colonic carcinomas" (see entire document, especially the Abstract).

The art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess, Annals of Oncology, Vol. 15, pages 1731-1737, 2004; e.g., paragraph bridging pages 1732-1733). In the instant case, the specification uses gene expression analysis to as a screening tool to identify genes of interest, and to obtain insight into an important biological function. However, the claims are drawn to using gene expression analysis to diagnose colorectal polyps and colorectal carcinoma. Pusztai and Hess teach that validation of gene expression important to biological function may be validated by using different methods, such as RT-PCR, whereas the most appropriate validation for using gene expression analysis as a classification tool is testing the predictor on independent sets of cases (e.g., page 1733, left column, 1st full paragraph). In the instant case the specification and declaration of Dr. Lee, filed 12/27/2007, provide an analysis by RT-PCR, but do not test the predictor on a set of cases.

Further, Shalon et al (US 2001/0051344 A1, Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (e.g., paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data

showing a statistical elevation or reduction in report levels when compared to control levels (e.g., paragraph [0156]). Pusztai and Hess teach that larger samples sizes may be needed to validate classification tests, and the number of samples will vary depending upon the acceptable error rates, level of inter-patient variability, the size of the difference in mean expression values, and the prevalence of the phenotype among the group being tested (e.g., page 1734, paragraph bridging columns; Table 1).

The prior art reveals that differences in gene expression observed between two groups are do not necessarily provide markers that can be used to reliably classify a subject. Golub et al (Science, Bol. 286, pages 531-537, October 1999) teach the use of a two-step procedure to test the validity of gene expression levels as predictors: step 1 involves cross-validation of the predictors on the initial data set, where one withholds a samples, builds a predictor based only on the remaining samples and predicts the class of the withheld sample; step 2 involves the repetition of assessing the clinical accuracy of the predictor set on an independent set of samples (e.g., page 532, right column). Although Golub et al could detect gene expression differences between chemotherapy responders and non-responders, those differences could not be use to predictably classify individuals (e.g., page 533, paragraph bridging left and middle columns). Accordingly, the art demonstrates the unpredictable nature of extrapolating gene expression differences to a method of class prediction.

Thus, the state of the art is underdeveloped with respect to the use of nucleic acids to diagnose and manage disorders in general; the state of the art is also underdeveloped with respect to the use of nucleic acids for the management of patient care and discovery of therapeutic interventions for CRC and colorectal polyps in particular.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, one of ordinary skill would not be able to make and use the full scope of the invention now claimed and as asserted in the application without undue experimentation. The specification discloses a single panel of genes exhibiting altered expression in a mouse model comprising a chemically induced mutation in the APC gene and normal control littermates for which there was not aberration of the APC gene and analysis of a panel of six biomarkers applied to samples obtained from patients known to have CRC and from normal controls. The application also discloses differences in expression of three biomarkers in biopsy samples taken from one exemplary patient diagnosed with CRC.

Based on this disclosure, the application seeks to claim a method comprising measuring expression of any panel of biomarkers comprising any two polynucleotides selected from SEQ ID NO: 1, 2 and 5 expressed in a biological colorectal sample and comparing such expression levels to control biological colorectal sample, wherein the comparison is determinative (i.e., diagnostic) of colorectal cancer and colorectal polyps or risk and is used in any aspect of the management of patient care in colorectal cancer and colorectal polyps, or such that the comparison is used in the discovery of any therapeutic intervention of colorectal cancer and colorectal polyps.

However, the art cited above clearly evidences that establishing expression of any single gene in any given cell system as a valid biomarker for any given condition is highly unpredictable and requires careful validation. This is acknowledged in the instant specification, which teaches that, "there is a distinct difference between research on a specific a gene, its expression, protein product, and regulation, and understanding what genes are critical to include

in a panel used to for the analysis of CRC that is useful in the management of patient care for the disease." (*Id.*) and that "given the complexity of biological systems, discovery of panels useful in providing value in patient care management for CRC is in the nascent stage" (*Id.*). In addition, as discussed above, the application teaches that there is substantial variation in expression levels of individual genes when compared with control sample (paragraph 0027), which necessitates the use of a panel of biomarkers for diagnostic validity.

Given the nascent and unpredictable state of the relevant art, one of ordinary skill would be required to empirically determine which panels of biomarkers and which biological samples within the expansive scope of the instant claims could be used to determine or indicate colorectal cancer and/or colorectal polyps in any given subject. Furthermore, one would be required to establish how RNA expression from genes of any given panel of biomarkers in any given biological sample correlates with any aspect of the management, such as risk assessment, early diagnosis, establishing prognosis, monitoring patient treatment, and detecting relapse. In view of the complex nature of the invention and the underdeveloped state of the art at the time of filing, which is acknowledged in Applicant's own specification, and the broad scope of the claims, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. Even for claims specifically reciting SEQ ID NOs: 1, 2, 5, 15 and 16 with particular samples from diseased tissue, one would have to establish that the differences in expression were statistically significant reliably correlated with the presence of colorectal cancer and polyps, risk assessment, prognosis and therapeutic effect. This would include analysis of the different levels of expression in a large number of individuals to establish the use of RNA

expression levels of the claimed biomarkers as class predictors for colorectal polyps and colorectal carcinoma.

In view of the foregoing, the skilled artisan would not be able to make and use the invention presently claimed without first engaging in undue experimentation. Therefore, the claims are properly rejected under 35 USC § 112, first paragraph, as lacking an enabling disclosure.

Claims 79 and 81-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

In the reply filed 7/8/2009, independent claim 79 was amended to require the kit for assessing the risk of colorectal cancer and colorectal polyps to include "a control comprising a normal level of a biomarker in a colorectal sample." However, the originally filed specification does not disclose kit comprising such a control. Paragraph [0038] provides support for instructions that include the step of "comparing the cDNA levels quantified to a control." The specification does not describe a "control comprising a normal level of a biomarker in a colorectal sample" in a kit.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the

specification and claims as originally filed, and Applicant has not provided passages that provide support.

Response to Arguments - 35 USC § 112

The rejection of claims 58 and 60 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 7/8/2009.

The rejection of claims 79 and 81-88 under 35 U.S.C. 112, first paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/8/2009.

With respect to the rejection of claims 49, 51-55, 57, 61-64 and 96-107 under 35 U.S.C. 112, first paragraph, Applicant's arguments filed 7/8/2008 have been fully considered but they are not persuasive.

The response asserts that new claim 98 sets for the subject matter indicated as enabled in the rejection made 1/8/2009. Thus, the response asserts that claims 98-107 are allowable. This argument is not found persuasive, because claim 98 is not commensurate in scope with the enabled scope indicated at pages 6-7 of the Office action mailed 1/8/2009. The enabled scope is directed to quantifying RNA expression levels for SEQ ID NO: 1 and SEQ ID NO: 2. Claim 98 is broader in scope in that it reads on quantifying expression levels for SEQ ID NO: 1 or SEQ ID NO: 2. The enabled scope is drawn to comparing a sample from a single subject with a group of control samples. Claim 98 is drawn to the comparison of a sample from a single subject with a sample from a single control. The enabled scope is drawn to determining increased risk of colorectal polyps and colorectal cancer in the subject when at least one of SEQ ID NOs: 1 and 2 is increased in expression in the sample from the subject as compared to normal controls. The

final "wherein" clause of claim 98 is drawn to indicating a colorectal cancer (diagnosis) rather than risk assessment, even though the preamble makes reference to assessing risk. Furthermore, claim 98 encompasses any increase or decrease in expression of SEQ ID NO: 1 or SEQ ID NO: 2 to indicate the presence or absence of colorectal cancer in the subject. Thus, claim 98 and claims that depend therefrom are broader in scope than what was indicated as being enabled in the Office action mailed 1/8/2009.

The response asserts that claim 49 has been amended consistent with the Examiner's indication that the disclosure is enabled for "risk assessment" and concludes that "management" of a subject following risk assessment by performing early diagnosis, establishing prognosis, monitoring patient treatment, and detecting relapse would also be enabled. This argument is not found persuasive. The enabled scope was recited at pages 6-7 of the Office action mailed 1/8/2009. Claim 49 is not commensurate in scope with the enabled scope. The specification does not teach what differences in expression of SEQ ID NOs: 1, 2 or 5 can be used in order to perform early diagnosis, establishing a prognosis, monitoring patient treatment or detecting relapse. The response does not provide evidence that the claimed methods of "management" were enabled by the prior art.

The response includes Exhibits A and B, which are asserted to be references that further demonstrate the methods and enablement of the disclosure with regard to the use of a panel of biomarkers for identifying subjects with polyps or colorectal cancer. The response notes that Table 5 of Lu et al (Exhibit A) indicates that 21 out of 25 subjects with polyps had altered gene expression compared to control subjects when using a minimally-invasive method, and 20 out of 25 subjects demonstrated altered gene expression compared to control using a biopsy method.

The response asserts that Exhibit A provides evidence that "using a panel of biomarkers of the disclosure, a subject having or at risk of having polyps could be identified more than 80% of the time." Moreover, the response notes that the reference indicates that up to 14 genes were differentially expressed in the cancer group, and COX2 (SEQ ID NO: 2), interleukin-8 (SEQ ID NO: 1), and CXCR2 (SEQ ID NO: 3) were among the more prevalent genes to be altered in the polyps of the FH/SH groups.

The evidence presented in Exhibit A is not sufficient to overcome the rejection of record, because it is not commensurate in scope with the claimed invention. The claims are not limited to determining risk of having polyps. Independent claim 49 requires the expression levels to be "indicative of colorectal cancer and polyps." Independent claim 98 requires the expression levels to be "indicative of colorectal cancer." Independent claim 107 is drawn to the "determination of colorectal cancer." Furthermore, the Lu et al reference relies upon a panel of genes, which is not commensurate in scope with the elected invention. For example, independent claims 98 and 107 read on the use of a single marker to make the determination of colorectal cancer. Lu et al teach that "no single gene was reliably able to distinguish risk of colon cancer from controls" (page 723, left column, 1st paragraph). Even if the claims were drawn to assessment of risk of polyps, the teachings of Lu et al would not enable the claimed invention, where SEQ ID NO: 1 and 2 are not measured. Also see the discussion at page 25 of the Office action mailed 1/8/2009 with regard to the biomarkers of SEQ ID NOs: 5, 15 and 16.

The response asserts that the expression of a single gene can be used as a valid biomarker for colorectal cancer. Specifically, the response asserts that Rubie et al provide evidence that IL-8 is useful as a prognostic and diagnostic marker. This argument is not found persuasive,

because Lu et al specifically included IL-8 as a biomarker in their study, yet they concluded that "no single gene was reliably able to distinguish risk of colon cancer from controls" (page 723, left column, 1st paragraph). The evidence on the record establishes the unpredictability of using a single biomarker for risk assessment or diagnosis.

The response notes that claim 49 was amended to indicate that the measurements can be analyzed using a MANOVA statistical technique to indicate a change compared to a control as indicative of colorectal cancer. The response asserts that this amendment was made to address how the quantification of biomarkers of the disclosure would predict or diagnose. This argument is not found persuasive. Even if one uses MANOVA, the claims encompass an increase or decrease in expression to indicate colorectal cancer and/or polyps.

In view of the evidence considered as a whole, it is concluded that the evidence fails to establish that one of skill in the art would have been enabled to make and use the full scope of the invention presently claimed without undue experimentation. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 79 and 81-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al (WO 2003/078662 A1; see the entire reference) in view of Gould et al (Kidney International, Vol. 61, pages 51-60, January 2002; see the entire reference), Goltry et al. (US Patent No. 6,025,336; see the entire reference), GenBank Accession No. M23698 (GI: 758678, publicly available April 1995; see the entire reference), Buck et al (Biotechniques, Vol. 27, No. 3, pages 528-536, 1999, cited on the IDS filed 4/2/2007; see the entire reference), and Ahern et al (The Scientist, Vol. 9, Issue 15, page 20, July 1995; see the entire reference). This rejection was made in the Office action mailed 1/8/2009. The rejection has been rewritten to address the new limitation of "control comprising a normal level of a biomarker in a colorectal sample."

Claim 79 is drawn to a kit comprising at least one reagent, which is oligonucleotides comprising the sequences set forth in SEQ ID NO: 45, 46, 47, 48, 53 and 54; control comprising a normal level of a biomarker in a colorectal sample; and instructions for using the kit for analyzing polynucleotide expression levels. The preamble of the claim merely recites the purpose of a process and the intended use, and the body of the claim does not depend on the preamble for completeness. The structural limitations of the body of the claim are able to stand

alone. Claims 81-83 further modify the preamble of the claim and content of instructions. Claim 84 is limits the oligonucleotides to at least two sets of primers chosen from (i) SEQ ID NO: 45 and 46; (ii) SEQ ID NO: 47 and 48; (iii) SEQ ID NO: 53 and 54; (iv) SEQ ID NO: 73 and 74); and (v) SEQ ID NO: 75 and 76 (i.e., at least two sets of primers that consist of the recited sequences). Claim 85 further requires reagents for the preparation of cDNA. Claim 86 further requires a reagent that is used for detection and quantification of polynucleotides. Claim 87 limits the reagent to one that includes at least one chromophore.

Baker et al teach a panel of two or more gene specific primers selected from the group consisting of the forward and reverse primers listed in Table 2 (e.g., page 18, lines 3-4). Table 2 contains forward and reverse primers for COX2 (PTGS2), which consist of SEQ ID NOs: 229 and 230 (e.g., Table 2 at page 72). The sequences of Baker et al, SEQ ID NOs: 229 and 230 consist of sequences 100% identical to the claimed sequences of SEQ ID NOs: 47 and 48 (see the attached alignments in Exhibits I and II). Baker et al teach that the primers may be used for gene expression profiling using RT-PCR preceded by an amplification step (e.g., page 5, lines 22-27; page 7, lines 7-9 and 25). Further, Baker et al teach RT-PCR of IL8 (e.g., page 8, lines 31-33). Baker et al teach further reagents for RT-PCR, including reagents for the preparation of cDNA, such as the GeneAmp RNA PCR kit; and reagents for the detection and quantitation of polynucleotides that contain at least one chromophore, such as components for TaqMan PCR® where the probe is designed to detect a nucleotide sequence between the two primers and is labeled with a reporter fluorescent dye (e.g., pages 31-32). Baker et al teach that RT-PCR is a flexible and quantitative method that can be used to compare mRNA levels in different sample populations, tumor tissues, including colon cancer, and corresponding normal tissues to

characterize patters of gene expression (e.g., page 4, lines 14-18; page 5, lines 18-21; page 7, lines 12-16; page 31, lines 12-18; page 31, lines 8-11). Thus, Baker et al teach normal colon tissue, and normal colon tissue would necessarily have a normal level of any biomarker.

Baker et al do not teach oligonucleotides to amplify the IL8 mRNA that consist of instant SEQ ID NOs: 45 and 46 and do not teach oligonucleotides comprising SEQ ID NOs: 53 and 54 (sequences of SAA1). Further, Baker et al do not specifically teach the components in kit form with instructions.

Gould et al teach oligonucleotides to be used as primers for RT-PCR of IL8 (e.g., Table 1). The forward primer for IL8 is 5'-AGATATTGCACGGGAGAATATACAAA-3', and the reverse primer for IL8 is 5'-TCAATTCCTGAAATTAAAGTTCGGATA-3' (Table 1). The primer sequences taught by Gould et al, consist of a nucleic acid sequence 100% to SEQ ID NOs: 45 and 46.

Goltry et al teach that specific oligonucleotide primers are generated for SAA1 to perform RT-PCR in samples, including samples obtained from patients who have been exposed to ionizing radiation for the treatment of solid tumors such as breast cancer (e.g., column 6, lines 22-43). Goltry et al teach a kit comprising primers specific for a particular gene or gene fragment, reagents for RT-PCR analysis, and instructions for using the primers and the reagents in an assay (e.g., paragraph bridging columns 6-7). Goltry et al teach a primer that consists of the human SAA1 sequence of CTCGGGACATGTGGAGAGCCTACTCTATTAGATACCCATTGTGTACCCTCT (e.g., Table 4), which comprises the sequence of instant SEQ ID NO: 53 (underlined portion).

GenBank Accession No. M23698 teaches the sequence of the human serum amyloid A1 (SAA1) mRNA, which comprises instant SEQ ID NOs: 53 and 54.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (e.g., page 532, column 3), with 69 different primers being submitted (e.g., page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (e.g., page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (e.g., page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (e.g., page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (e.g., page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Ahern et al teach that packaging reagents in kit format is convenient, offering the scientists the opportunity to better manage their time. Ahern et al teach that premade reagents and packaged kits, including detailed instructions, saves researchers time (e.g., pages 4/5-5/5).

Because both Baker et al and Gould et al teach primers for RT-PCR of IL8, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute

the specific IL8 primers of Gould et al for the unspecified IL8 primers of Baker et al in order to achieve the predictable result of providing primers for the amplification of IL8 cDNA obtained from mRNA. One would have been motivated to use the primers of Grould et al, because they were shown in the art to perform such a function. The primers of Gould et al consist of instant SEQ ID NOs: 45 and 46.

Because both Baker et al and Goltry et al teach providing primers for RT-PCR of mRNA obtained from breast cancer subjects, it would have been obvious to one of ordinary skill in the art to include primers for amplification of SAA1, as taught by Goltry et al. One would have specifically included the disclosed forward primer of Goltry et al (comprising instant SEQ ID NO: 53). Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further include a reverse primer for SAA1, because Baker et al teach RT-PCR with a forward primer and reverse primer. To provide such a reverse primer, the skilled artisan would have looked to the known SAA1 mRNA sequence taught by GenBank Accession No. M23698, which comprises both instant SEQ ID NOs: 53 and 54. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to primers for PCR. The ordinary artisan would be motivated to have designed and tested new primers or probes to obtain additional oligonucleotides that function to amplify SAA1, including primers comprising instant SEQ ID NO: 54. Moreover, it would have been obvious to one of skill in the art to combine the primers and reagents in kit form with instructions, because Baker et al, and Goltry et al teach reagents for RT-PCR in kit form, and Ahern et al teach that kits including detailed instructions saves researchers time.

One would have been motivated to make such modifications in order to receive the expected benefit of expanding the repertoire of primers available to perform RT-PCR and to provide such reagents in a form that saves time as taught by Ahern et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 88 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al (WO 2003/078662 A1; see the entire reference) in view of Gould et al (Kidney International, Vol. 61, pages 51-60, January 2002; see the entire reference), Goltry et al. (US Patent No. 6,025,336; see the entire reference), GenBank Accession No. M23698 (GI: 758678, publicly available April 1995; see the entire reference), Buck et al (Biotechniques, Vol. 27, No. 3, pages 528-536, 1999, cited on the IDS filed 4/2/2007; see the entire reference), and Ahern et al (The Scientist, Vol. 9, Issue 15, page 20, July 1995; see the entire reference) as applied to claims 79 and 81-87 above, and further in view of Qiagen News (Issue 2, pages 1-13, 1998; see the entire reference). This is a new rejection.

The teachings of Baker et al, Gould et al, Goltry et al, GenBank Accession No. M23698, Buck et al, and Ahern et al are described above and applied as before. Further, Baker et al teach the use of RNeasy^{TM} Mini kit for RNA isolation for use in RT-PCR.

Baker et al, Gould et al, Goltry et al, GenBank Accession No. M23698, Buck et al, and Ahern et al do not explicitly teach labware for at least one of sample collection, sample preparation or sample analysis.

Qiagen News teaches RNeasy Mini Kits comprising RNeasy mini spin columns, collection tubes, and RNase-free reagents and buffers (e.g., page 13). Further, Qiagen News teaches that RNeasy can be used for the synthesis of high quality cDNA from RNA isolated from breast tumor biopsy tissue (e.g.., page 12).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify combined the teachings of Baker et al, Gould et al, Goltry et al, GenBank Accession No. M23698, Buck et al, and Ahern et al to include the RNeasy kit components including labware from sample preparation taught by Qiagen News because Baker et al teach it is within the ordinary skill in the art to use RNeasy for sample preparation and Qiagen News teach the RNeasy kit components.

One would have been motivated to make such a modification in order to receive the expected benefit of providing reagents capable of high quality cDNA from tissues of interest including breast tumor biopsy tissue as taught by Qiagen News. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

Applicant's arguments filed 7/8/2009 have been fully considered but they are not persuasive.

The response asserts that the references do not teach or suggest (i) a kit comprising a normal colorectal amount of a biomarker, or (ii) instructions for measuring the expression level for risk assessment.

With regard to the "control comprising a normal level of a biomarker in a colorectal sample," this limitation is met by the teachings of Baker et al. Baker et al teach that RT-PCR is a flexible and quantitative method that can be used to compare mRNA levels in different sample populations, tumor tissues, including colon cancer, and corresponding normal tissues to characterize patters of gene expression (e.g., page 4, lines 14-18; page 5, lines 18-21; page 7, lines 12-16; page 31, lines 12-18; page 31, lines 8-11). Thus, Baker et al teach normal colon tissue, and normal colon tissue would necessarily have a normal level of any biomarker.

With regard to the instructions for measuring the expression level for risk assessment, Ahern et al teach that packaging reagents in kit format is convenient, offering the scientists the opportunity to better manage their time. Ahern et al teach that premade reagents and packaged kits, including detailed instructions, saves researchers time (e.g., pages 4/5-5/5). Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004). There is no new and unobvious functional relationship between the printed matter and the contents of the kit. Ahern teaches that detailed instructions are provided to allow one to easily use the packaged materials. Instructions in the claimed kit would serve the same function (e.g., specification, paragraph [0038]).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston
Examiner
Art Unit 1636

/JD/

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636